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Date: March 21, 2006

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Subject: Paper: Appeal Brief
Serial No.: 09/888,126
Filing Date: June 22, 2001
Appellants: Jennifer L. Schmitke, *et al.*
EPLG Docket No.: 2685.2030 US(000)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/888,126	Confirmation No.: 9053
Appellants	: Jennifer L. Schmitke, Donghao Chen, Richard P. Batycky, David A. Edwards and Jeffrey S. Hrkach	
Filed	: June 22, 2001	
TC/A.U.	: 1616	
Examiner	: Mina Haghighatian	
Docket No.	: 2685.2030-000	
Customer No.	: 000038421	
Title	: Particles for Inhalation Having Rapid Release Properties	

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APPEAL BRIEF

Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal received in the U.S Patent and Trademark Office on April 28, 2005, and in support of the appeal from the final rejection(s) set forth in the Office Action mailed on January 11, 2005. The fee for filing a brief in support of an appeal was filed on June 28, 2005.

(i) Real party of interest

The real party of interest in this appeal is Advanced Inhalation Research, Inc. by virtue of Assignment recorded on January 22, 2002 at Reel 012544 and frame 0581.

(ii) Related appeals and interferences

There is a related appeal in U.S. Pat App. No. 10/179,463. A notice of appeal was filed in the related application on April 14, 2005. A Brief on Appeal is being filed in the related application on even date herewith. No decision on the merits has been received at this time.

(iii) Status of claims

Claims 1, 3-18, 20-39 and 41-60 are pending, finally rejected and appealed. Claims 2, 19, and 40 were previously canceled.

(iv) Status of amendments

No amendment after final rejection has been filed. A Reply After Final Rejection was filed on March 10, 2005.

(v) Summary of claimed subject matter

The invention relates to a novel insulin-containing formulation. Independent Claim 1 is directed to a formulation comprising particles having, by weight, approximately 60% DPPC, approximately 30% insulin, and approximately 10% sodium citrate. See also page 3, lines 9-11. This formulation was chosen for its superior fast acting properties, and superior stability and manufacturability. Independent Claim 18 provides a method for treating a human patient in need of insulin comprising administering, in a single breath, the formulation discussed above via delivery to the pulmonary system. See also page 3, lines 18-23. Independent Claim 39 provides a method for administering insulin to the pulmonary system comprising providing the formulation discussed above and inhaling the same from a breath actuated inhaler. See also page 3, lines 24-28.

(vi) Ground of rejection to be reviewed

The sole ground of rejection to be reviewed on appeal is whether the Examiner has established a *prima facie* case of obviousness of one or all claims over Patton et al.,

U.S. Patent No. 5,997,848 ("Patton") in view of Edwards et al., U.S. Patent No. 5,985,309 ("Edwards").

(vii) Argument

Claims 1, 3-18, 20-39 and 41-60

In the Final Office Action, the Examiner relies upon Patton to teach dry powder insulin that can be administered to a mammal, resulting in a systemic delivery characterized by rapid absorption. The rejection states that the product can be prepared by dissolving insulin in an aqueous buffer (such as a citrate buffer) and spray drying the solution to produce amorphous particles having "a particle size less than 10 microns." According to the rejection, preferred carriers disclosed by Patton include amino acids, such as glycine, lysine, etc. The Examiner notes that insulin and carrier concentrations can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. The Examiner notes, however, that Patton does not teach the use of DPPC as a carrier.

The Examiner turns to Edwards to establish that surfactants, such as DPPC, are known in the manufacture of insulin-containing inhalation products. The Examiner suggests that the person of ordinary skill in the art would be motivated to modify the formulations of Patton to use DPPC, as taught by Edwards, because DPPC was known to be a natural lung surfactant.

Even if the Examiner has established a *prima facie* case of obviousness (i.e. that it would be obvious to substitute some or all of Patton's insulin, buffer, and/or carrier for Edward's DPPC), the evidence of record, presented in the enclosed Rule 132 Declaration, establishes significant unexpected results. Thus, the selection of the presently claimed approximate amounts of 60% DPPC, 30% insulin and 10% citrate combination is patentable over the myriad of possible combinations derived from the combination of Patton and Edwards.

It is well settled that unexpected results can be established by factual evidence. *In re Lindner*, 173 USPQ 356 (CCPA 1972). Appellants have provided this factual evidence in the form of a Rule 132 declaration. It is also well settled that proof of

unexpected properties may be in the form of direct or indirect comparative testing of the claimed compounds and the closest prior art. See, for example, *In re Payne*, 203 USPQ 245, 256 (CCPA 1979); *In re Grasselli*, 218 USPQ 769 (CAFC 1983) and *In re Fenn*, 639 F.2d 762, 208 USPQ 470 (CCPA 1981). In *In re Fenn*, the court approved the use of declaratory evidence showing an indirect comparison between the appellant's diaphragm prepared according to appellant's specification and the swelling characteristics of the closest prior art which was sufficient to provide an indirect showing of unexpected superiority sufficient to rebut a *prima facie* case of obviousness.

In the Final Office Action, the Examiner does not appear to contest the sufficiency of Appellants' declaratory evidence or the unexpected superiority of the results provided therein other than to state that the declaratory evidence is "not found persuasive". The Examiner simply maintained the obviousness rejection without any real articulated rationale or evidentiary support as to *why* Appellants' comparative data is insufficient to rebut the Examiner's obviousness objection, in contrast to the directives set forth in MPEP 2144.08 (III). On page 3 of the Final Office Action, the Examiner states that:

> "[the Declaration] was not found persuasive because while it provided data on the stability of certain concentration ranges, it did not overcome the prior art rejections. While applicant insists that the specific amounts of each ingredient makes the formulations stable, the concentration ranges fall within the ranges disclosed by the references and thus it is considered that the prior art of record meets the claimed limitations."

Thus, it appears from this statement that the mere fact that, with respect to the individual components of the formulation that are taught in each of the two references, the references teach broad ranges (e.g., Patton teaches between 20 – 80 % insulin and 80 - 20% excipients) generically embracing the specific amounts selected by Appellants (approx. 30% insulin, 60% DPPC and 10% citrate), evidence of unexpected results are irrelevant. Of course, this is untrue, as clearly established by the caselaw discussed above. Even where a single reference generically describes a species (which is not the

rejection asserted by the Examiner in this case), evidence of unexpected results can rebut an obviousness rejection and result in patentability.

In the Advisory Action, the Examiner apparently attempts to contest the sufficiency of Appellants' declaratory evidence. The Examiner states that:

> "While it is accepted that Applicant's declaration shows certain properties of formulations having different ratios of DPPC:sodium citrate:insulin, it does not show significant unexpected results as Applicant claims. The figures that show different "crash out" times are not clearly showing a significant difference. Furthermore the Declaration fails to recite side by side comparisons of the instant formulations with those of the prior art and thus do not overcome the prior art rejection."

In the Examiner's Answer dated September 20, 2005, the Examiner points to the statement from the title of Figure 2. The results pointed to the fact that DPPC concentration is not the sole predictor of the insulin formulation, but in fact a critical balance of insulin, DPPC and solution concentration achieved the formulation. Figure 2, for example, shows that 10% insulin formulations "crash out" of solution rapidly, ranging from 5 minutes to two hours depending upon the concentration of insulin comprising the 10% formulation. On the other hand, the 30% insulin formulation does not crash out of solution *at all*. In other words, at concentrations as low as 10 g/L of the total solids (DPPC/insulin/citrate; 4 g/L of DPPC), the 10% insulin containing formulation was unstable compared to the 30% insulin containing formulation where stability was observed even at 20 g/L of the total solids (12 g/L of DPPC). The Appellants did not understand the Examiner's point in the Answer when she states that "A rather exponential relationship between the amounts of insulin and stability." The Examiner has only looked at the data in a two dimensional point of view and did not consider the fact that the total concentrations of the total solids also play an important role. The improved solubility of the total solids is critical to stability, manufacturability and ultimately, the desired performance of the formulation.

The Examiner is simply incorrect about the lack of significance of the unexpected results described in the declaration. As discussed in the Appellants' declaration, this result would not have been predictable based solely on DPPC solubility (see Figure 1 of

the declaration) and results in a dramatic improvement in manufacturability of the formulation that could not have been predicted. The Examiner's conclusion that these results are not significant is simply unsubstantiated.

MPEP 2144.05 (III) states that "[a]pplicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range". Appellants' 132 declaration clearly shows that the criticality of the presently claimed formulation (not a *range* of formulations as described by the Examiner, but instead a superior *single species* of formulation), having particles comprising, by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate possesses unexpected properties as compared to formulations that are even *closer* than those of the combination of prior art cited by the Examiner. The Patton reference cited by the Examiner discloses that insulin and carrier concentrations can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. Patton makes no specific mention of the range of citrate. The Examiner relies on Edwards to provide DPPC as a carrier but no preferred DPPC range is disclosed in Edwards. In the Examples, Edwards describes a number of different DPPC-containing formulations, including formulations containing 10%, 33% and 60% by weight DPPC. Clearly, the combination of cited references provides so many possible combinations of formulations, that evidence of unexpected results (provided by Appellants' 132 declaration) for a *single* combination is more than sufficient to overcome any *prima facie* case of obviousness in view of the combined references. For example in *In re Ruschig*, 145 USPQ 274 (CCPA 1965), the court was faced with claimed species of compounds that fell into the general class of sulfonylureas, known to be a large class of compounds. The compounds singled out for patenting had been discovered by appellants as a part of their systematic and extensive research, to possess the ability to lower the level of blood sugar, for use in treating diabetes but also because of other desirable properties that they possess in connection with such use. Appellants provided a declaration indicating that as compared with compounds of similar structure to the claimed compounds, the claimed compounds are distinguishable based on a number of properties including shelf-life, handling and that they also have no bacteriostatic action as compared to similar anti-diabetic compounds.

The *Ruschig* court reversed the Patent Office's obviousness rejection and citing *In re Lunsford* 140 USPQ 425, 427 stated that:

> "and in *In re Lunsford*, 51 CCPA 1000, 327 F.2d 526, 140 USPQ 425, 427, wherein Judge Martin, speaking for the court, finding an "unobvious property inherent in the claimed compounds" sufficient to overcome a showing of very close structural obviousness, said "there is no basis in law for ignoring any property," and in *In re Ward*, 51 CCPA 1132, 329 F.2d. 1021, 141 USPQ 227, 228, wherein the court said:
>
> * * * claims to chemical compounds are drawn to more than structural formulae. They define the compounds themselves and compounds possess properties which must be considered along with the formulae.
>
> Here the esters might appear to be obvious in terms of the concept of their structure but that is only half the game. There remains the consideration of the properties of the esters. * * * That unexpected property cannot be ignored in the determination of obviousness of the claimed esters *as substances* and not as structural formulae."

The case law permits patenting a species even where the prior art generically discloses it based upon evidence of unexpected results. The MPEP states that patenting within ranges is permissible with sufficient evidence of unexpected results. MPEP 716.02 (d).

Clearly, Appellants' showing of unexpected enhanced stability and manufacturability of the presently claimed *specific* formulation is sufficient to overcome any *prima facie* case of obviousness in view of the potentially infinite combinations of formulations provided by the excipients and ranges disclosed in the cited combination of Patton and Edwards. Appellants have shown unexpected and enhanced stability as compared to formulations that are even *more* similar to those of cited prior art in their 132 declaration.

With regard to the Examiner's statement in the Final Office Action that "[i]t is also noted that stability is a property of the formulations", Appellants are unclear as to what the Examiner's point is here. If the Examiner is asserting that because stability is a property of any formulation, a showing of unexpected superiority in that property in the claimed embodiment is insufficient to overcome obviousness, the position is illogical and contradicts established case law. Indeed, the case law discussed herein establishes that

evidence of unexpected results in the properties of a claimed product can be relied upon to rebut a prima facie case of obviousness.

For example in *In re Chupp*, 2 USPQ2d 1437, the Appellant (Chupp) submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art compounds and with two commercial herbicides, to rebut the prima facie case of obviousness. The tests compared the compounds' ability to control two weeds and it was undisputed in the record that the claimed compound gave superior results. The board deemed the declaratory evidence insufficient to rebut the case of obviousness claiming the compound had no new or unexpected property; it possesses the same property as the prior art compounds. The court, citing *In re Papesh*, 137 USPQ 43 (CCPA 1963), reversed and stated that:

> "The Papesch court held, "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing" (citation omitted). Under the Papesch doctrine, evidence of unobvious or unexpected advantageous properties may rebut a prima facie case of obviousness based on structural similarities [citation omitted]. Such evidence may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds. E.g. *In re Lunsford*, 357 F2d 380, 148 USPQ 716 (CCPA 1966). "

The court in *In re Chupp* went on to cite another case, *In re Ackerman*, 170 USPQ 340 at 343 (CCPA 1979) for additional precedent indicating that "evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a prima facie case of obviousness". Although the Solicitor in *Chupp* tried to argue that *Chupp*'s declaratory evidence did not show an unexpected difference in the properties in view of the prior art, the court disagreed. The court noted that the record did not support the Solicitor's assertion that the claimed compound's superior properties would have been expected, and to support the court's position, the court cited *In re Blondel*, 499 F2d 1311,182 USPQ 294 (CCPA 1974) (reversing rejection of claims to compounds which prior art suggested would have longer lasting pharmacological activity, where actual increase was beyond reasonable expectations).

Similarly, in the present application, the Examiner has provided no evidence that the superiority of the stability properties of the claimed formulation as described in

Appellants' 132 declaration are in any way predicted or suggested in the cited combination of prior art. Neither reference discusses the criticality of the amounts of each component of the formulation to provide superior stability and manufacturability.

Perhaps the Examiner is concerned by the fact that the evidence of record compares, not the specific formulations of Patton, but more relevant or closer formulations provided by Appellants. The courts have looked favorably upon indirect evidence that is even closer than that of the prior art. For example, in *In re Grasselli, supra*, an applicant claiming a catalyst showed unexpected results when he tested the claimed catalyst with the more similar catalysts, which were his own, that were claimed in broader claims. The court found that none of the prior art cited by the examiner described a catalyst more similar to the claimed catalyst than the Appellants' own catalysts claimed in the broader claims. See 218 USPQ at 779. The *Grasselli* court found this indirect showing of superiority over the prior art sufficient to rebut the Examiner's showing of obviousness.

Similarly, in the present application, neither Patton nor Edwards cited by the Examiner, provides an example of a formulation comprising all the components of the presently claimed formulation, i.e. DPPC, insulin and sodium citrate. Appellants have instead provided formulations for comparison that are *closer* than those of the cited combination of prior art. The Declaration shows that six formulations that differ solely in the relevant amounts of the hydrophobic component (e.g., DPPC), citrate and insulin can have substantial differences in stability and manufacturability. Notably, increasing the amount of insulin in the formulation from 10% to 30%, with a corresponding decrease in the lipid (i.e. "hydrophobic") component, DPPC, dramatically and unexpectedly improved the solubility of the total solids in the spray drying solution. The improved solubility of total solids is critical to the stability, manufacturability and ultimately, the desired performance of the formulation. Therefore, Appellants have met the burden of providing comparative data with the closest prior art by making an indirect showing of unexpected superiority using prior art that is even closer than the prior art provided by the Examiner.

In view of the above arguments and citation of case law, Appellants submit that they have provided evidence in the form of a 132 declaration sufficient to meet their burden of establishing unexpected and significant properties of the presently claimed formulation. Thereby, Appellants submit that they have rebutted any *prima facie* case of obviousness that the Examiner may have established by the combination of cited references and respectfully request that the rejection under 35 U.S.C. §103 over Patton in view of Edwards be reversed.

Claims 18, 20-39, and 41-57

If the Examiner finds Claim 1 allowable, then all claims are allowable as uses of a novel particle formulation and all claims dependent thereon. Even if Claim 1 is not allowable, Claim 18 (and the claims dependent therefrom) are separately allowable because claim 18 recites that the formulation is administered to the patient in a single, breath-actuated step, a limitation not disclosed by Patton or Edwards. The Examiner's conclusion that this is obvious is unsupported by the record. Similarly, Claim 39 (and the claims dependent therefrom) recites simultaneous inhalation and dispersion of the particles from a receptacle containing the particles (e.g., breath actuated administration). Neither Patton nor Edwards disclose or make obvious this feature which is unique to the presently claimed particle formulation.

Application No.: 09/888,126

Summary

Appellants' declaration providing unexpected results overcomes the Examiner's rejection of the claims as being *prima facie* obvious over Patton in view of Edwards. The Examiner has not provided any scientifically *accurate* evidence or rationale for claiming that Appellants' declaration is insufficient. Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

ELMORE, CRAIG & VANSTONE, P.C.

By [signature]
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Chelmsford, MA 01863
Dated: 3/20/06

Application No.: 09/888,126

(viii) CLAIMS INDEX

Claims as of 4/20/04

1. (original) A formulation having particles comprising, by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate.

2. canceled.

3. (previously amended) The formulation of Claim 1, wherein the particles comprise a mass of from about 1.5 mg to about 20 mg of insulin.

4. (previously amended) The formulation of Claim 1, wherein the particles are placed in a receptacle and comprise a mass of about 1.5 mg of insulin per receptacle.

5. (previously amended) The formulation of Claim 1, wherein the particles are placed in a receptacle and comprise a mass of about 5 mg of insulin per receptacle.

6. (original) The formulation of Claim 1, wherein the particles comprise a dosage of insulin of between about 42 IU and about 540 IU.

7. (original) The formulation of Claim 6, wherein the particles comprises a dosage of insulin of about 42 IU.

8. (original) The formulation of Claim 6, wherein the particles comprise a dosage of insulin of between about 84 IU and about 294 IU.

9. (original) The formulation of Claim 8, wherein the particles comprise a dosage of insulin of between about 155 IU and about 170 IU.

10. (original) The formulation of Claim 1, wherein the particles have a tap density less than about 0.4 g/cm^3.

11. (original) The formulation of Claim 10, wherein the particles have a tap density less than about 0.1 g/cm^3.

12. (previously amended) The formulation of Claim 1, wherein the particles have a median geometric diameter of from between about 5 micrometers to about 30 micrometers.

13. (original) The formulation of Claim 1, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 5 micrometers.

14. (previously amended) The formulation of Claim 13, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 3 micrometers.

15. (original) The formulation of Claim 13, wherein the particles have an aerodynamic diameter of from about 3 micrometers to about 5 micrometers.

16. (original) The formulation of Claim 1, wherein the particles further comprise an amino acid.

17. (original) The formulation of Claim 16, wherein the amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

18. (original) A method for treating a human patient in need of insulin comprising administering pulmonarily to the respiratory tract of a patient in need of treatment, in a single, breath actuated step an effective amount of particles comprising by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate, wherein release of the insulin is rapid.

19. canceled.

20. (original) The method of claim 18, wherein the patient in need of treatment has diabetes mellitus.

21. (previously amended) The method of Claim 18, wherein the particles have a mass of from about 1.5 mg to about 20 mg of insulin.

22. (original) The method of Claim 18, wherein the particles comprise a mass of about 1.5 mg of insulin per receptacle.

23. (previously amended) The method of Claim 18, wherein the particles are placed in a receptacle and comprise a mass of about 5 mg of insulin per receptacle.

24. (previously amended) The method of Claim 18, wherein the particles are placed in a receptacle and comprise a dosage of insulin of between about 42 IU and about 540 IU.

25. (original) The method of Claim 24, wherein the particles comprises a dosage of insulin of about 42 IU.

26. (original) The method of Claim 24, wherein the particles comprise a dosage of insulin of between about 84 IU and about 294 IU.

27. (original) The method of Claim 26, wherein the particles comprise a dosage of insulin of between about 155 IU and about 170 IU.

28. (original) The method of Claim 18, wherein the particles have a tap density less than about 0.4 g/cm^3.

29. (original) The method of Claim 28, wherein the particles have a tap density less than about 0.1 g/cm^3.

30. (previously amended) The method of Claim 18, wherein the particles have a median geometric diameter from about 5 micrometers to about 30 micrometers.

31. (original) The method of Claim 18, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 5 micrometers.

32. (previously amended) The method of Claim 31, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 3 micrometers.

33. (original) The method of Claim 31, wherein the particles have an aerodynamic diameter of from about 3 micrometers to about 5 micrometers.

34. (original) The method of Claim 18, wherein administering the particles pulmonarily includes delivery of the particles to the deep lung.

35. (original) The method of Claim 18, wherein administering the particles pulmonarily includes delivery of the particles to the central airways.

36. (previously amended) The method of Claim 18, wherein administering the particles pulmonarily includes delivery of the particles to the upper airways.

37. (original) The method of Claim 18, wherein the particles further comprise an amino acid.

38. (original) The method of Claim 37, wherein the amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

39. (original) A method of delivering an effective amount of insulin to the pulmonary system, comprising:
    a) providing a mass of particles comprising by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate; and
    b) administering via simultaneous dispersion and inhalation the particles, from a receptacle having the mass of the particles, to a human subject's respiratory tract, wherein release of the insulin is rapid.

40. canceled.

41. (previously amended) The method of Claim 39, wherein the mass of particles is from about 1.5 mg to about 20 mg of insulin.

42. (previously amended) The method of Claim 39, wherein the particles are placed in a receptacle and the mass of said particles comprises about 1.5 mg of insulin per receptacle.

43. (previously amended) The method of Claim 39, wherein the particles are placed in a receptacle and the mass of said particles comprises about 5 mg of insulin per receptacle.

44. (original) The method of Claim 39, wherein the mass of particles comprises a dosage of insulin of between about 42 IU and about 540 IU.

45. (original) The method of Claim 44, wherein the mass of particles comprises a dosage of insulin of about 42 IU.

46. (original) The method of Claim 44, wherein the mass of particles comprises a dosage of insulin of between about 84 IU and about 294 IU.

47. (original) The method of Claim 46, wherein the mass of particles comprises a dosage of insulin of between 155 IU and about 170 IU.

48. (original) The method of Claim 39, wherein the particles have a tap density less than about 0.4 g/cm^3.

49. (original) The method of Claim 48, wherein the particles have a tap density less than about 0.1 g/cm^3.

50. (previously amended) The method of Claim 39, wherein the particles have a median geometric diameter of from about 5 micrometers to about 30 micrometers.

51. (original) The method of Claim 39, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 5 micrometers.

52. (original) The method of Claim 50, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 3 micrometers.

53. (original) The method of Claim 50, wherein the particles have an aerodynamic diameter of from about 3 micrometers to about 5 micrometers.

54. (original) The method of Claim 39, wherein delivery to the pulmonary system includes delivery to the deep lung.

55. (original) The method of Claim 39, wherein delivery to the pulmonary system includes delivery to the central airways.

56. (original) The method of Claim 39, wherein delivery to the pulmonary system includes delivery to the upper airways.

57. (original) The method of Claim 39, wherein the particles further comprise an amino acid.

58. (original) The method of Claim 57, wherein the amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

59. (original) The formulation of Claim 1, wherein the particles further comprise a low transition temperature phospholipid.

60. (original) The method of Claim 18, wherein the particles further comprise a low transition temperature phospholipid.

(ix) EVIDENCE APPENDIX

1.132 Declaration of Jennifer L. Schmitke (attached)

VIDENCE APPENDIX

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Application No. :09/888,126 Confirmation No.:9053
Applicant :Jennifer L. Schmitke, Donghao Chen, Richard P. Batycky, David A. Edwards and Jeffrey S. Hrkach
Filed :June 22, 2001
TC/A.U. :1616
Examiner :Mina Haghighatian

Docket No. :2685.2030-000
Customer No. :

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April 30, 2004 Judy Breen
Date Signature

Judy Breen
Typed or printed name of person signing certificate

DECLARATION UNDER 37 CFR 1.132

Sir:

I, Jennifer L. Schmitke, of 476 Shawmut Ave. #5, Boston, Massachusetts 02218, am an inventor of the above identified application.

The invention which is described in the above identified application results from substantial experimentation that necessitated the selection of a formulation that achieves serum insulin levels similar to that achieved by injectable insulin, good to excellent bioavailability, good to excellent physical stability and good to excellent manufacturability. The formulation of Claim 1 unexpectedly accomplishes all of these

objectives. Below, I describe experiments that I conducted or were conducted under my supervision or direction.

1.0 Background

AIR Human Insulin Inhalation Powder (HIIP) is a spray-dried powder comprised of human insulin (BHI), sodium citrate, and DPPC (1, 2–Dipalmitoyl-*sn*-Glycero-3-Phosphocholine The HIIP manufacturing process involves two (2) liquid feed streams: an ethanol-based solution containing the surfactant DPPC, and an aqueous solution containing BHI and citric acid monohydrate. During the batch production process, the organic solution and the aqueous solution are continuously pumped to the spray dryer at a controlled 60/40 (organic/aqueous) volumetric ratio. The feed streams are individually pre-heated to ~50°C and then combined in an in-line static mixer just before entering the atomizer for the spray dryer.

The solubility of the combined organic/aqueous feed stream for the HIIP process was investigated to ensure that no solids would precipitate or "crash out" once the individual phases were combined. Any solids in the combined feed stream to the spray dryer could significantly impact solution atomization, and subsequently affect the aerosol performance of the HIIP product.

2.0 Objective

The primary objective of this study was to identify maximum solids concentrations for different compositions of Human Insulin Inhalation Powder (HIIP) formulations. The study characterized the varying solubility range for a combined 60/40 vol.% organic/aqueous feed solution at 50°C.

The secondary objective was to determine if holding the individual organic and aqueous phases stirring at room temperature over a period of eight hours (typical duration for a

manufacturing campaign) prior to combination affected the solubility of the 60/40 vol.% organic/aqueous feed solution.

3.0 Testing Methods

3.1 Solubility vs. Concentration and Composition

Several sets of solutions were prepared (Reference Appendix A for solution preparation procedures) at different solids concentrations and compositions as shown in the table below. All solutions were 60/40 vol.% ethanol/water.

Table 1: Compositions and Concentrations of Test Solutions

Solution Label	Wt.% Insulin	Wt.% DPPC	Wt.% Sodium Citrate	Total Solution Concentration (g/L)
10% Insulin	10	80	10	5
15% Insulin	15	75	10	5, 10, 15
20% Insulin	20	70	10	5, 10, 15
25% Insulin	25	65	10	15, 25
30% Insulin	30	60	10	8, 10, 11, 12, 15, 20
30% Insulin	30	60	10	25, 30, 40, 50

The organic and aqueous phases of each test solution were prepared at room temperature and then placed in a 50°C Water Bath for 30 minutes to an hour. The individual phases were combined once they reached the 50°C equilibration temperature. The combined solution was returned to the water bath, and then monitored visually until any particles were observed to "crash out" of solution.

3.2 Solution Solubility vs. Time

To investigate whether "aging" of the individual organic and aqueous phases could affect the solubility of the combined solution, aqueous and organic solutions were prepared and stirred at room temperature over an eight-hour period. The 60/30/10 weight percent DPPC/insulin/citrate formulation (i.e, 30% HIIP formulation) at a total solids concentration of 15 grams per liter was selected for this study. The preparation of these solutions is detailed in experiment 04-xxx-357-181 (notebook 357, page 181).

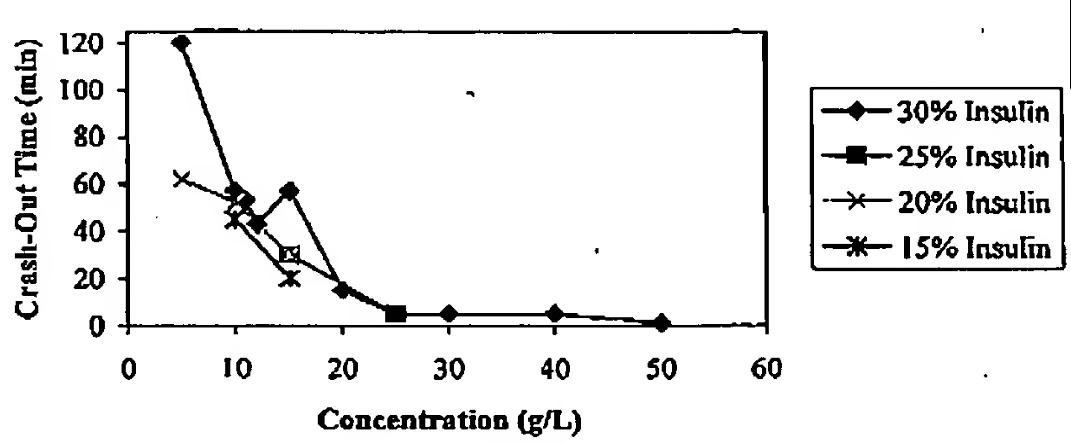
At times of 0 (fresh feed), 2, 4, 6 and 8 hours, a sixty milliliter (60 ml) sample was drawn from the organic phase and a forty milliliter (40 ml) sample was drawn from the aqueous phase. The aqueous and organic samples were placed into a 50°C Water Bath for 15 minutes to achieve temperature. The samples were then combined and returned to the water bath. The combined solution was monitored visually until particles were observed to "crash out" of solution.

4.0 Results and Discussion

4.1 Solubility vs. Concentration and Composition

Figure 1 shows "crash-out" time as a function of solids concentration and percent insulin composition. The higher the total solids concentration, the faster solids were observed to come out of the combined 60/40 vol% org/aq. solution. Although the 30% insulin formulation was not limited by solubility until it reached a concentration of 50 g/L, rapid

Figure 1
Concentration vs. "Crash-Out" Time



"crash-out" times (i.e., 5 minutes or less) were observed at concentrations of 25 g/l and higher.

Figure 2
Composition vs. "Crash-Out" Time

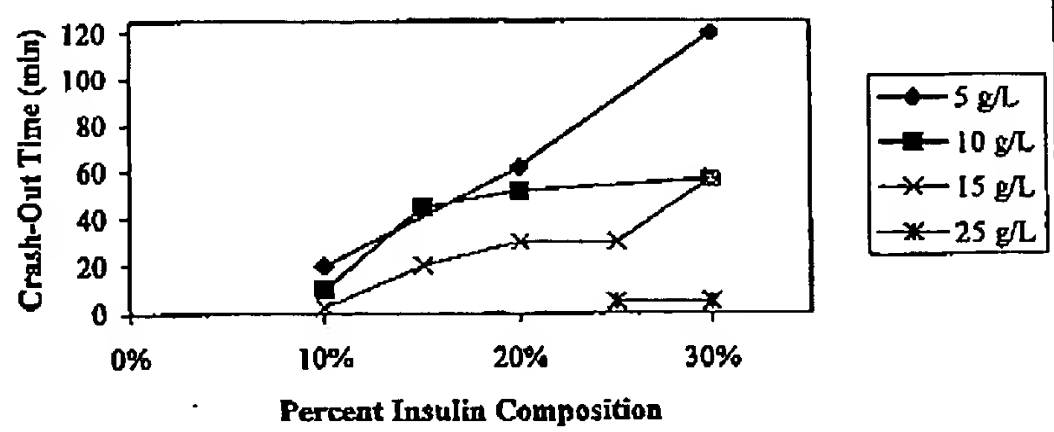


Figure 2 shows that higher insulin content solutions appear to stay in solution longer (i.e., have higher "crash-out" times). This could be because higher insulin content translates to a lower DPPC content (as seen in Table 1).

Figure 2 also shows that the 10% insulin formulation has rapid "crash-out" times (i.e., 5 minutes or less) for concentrations above 10 g/L. This observed drop in solubility as concentration increases makes the 10% insulin formulation an unattractive "low-load" insulin formulation from a process manufacturing point of view. The limits in feed solution solubility for the 10% insulin formulation would hence limit the possible solids throughput in the manufacturing scheme.

In other words, the 10% insulin formulation experienced rapid "crash-out" times with a DPPC concentration of 4.0 g/l, an insulin concentration of 0.5 g/l and a citrate concentration of 0.5 g/l. However, the 30% insulin formulation did not "crash-out" even at concentrations of 20 g/l total solids, resulting in a DPPC concentration of 12.0 g/l, an insulin concentration of 6 g/l and a citrate concentration of 2 g/l. Clearly, the solubility

of the insulin formulation is not dictated solely by DPPC solubility. Such a dramatic improvement in manufacturability could not have been predicted.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Jennifer L. Schmitke

Appendix A: General Solution Preparation

General solution preparation procedures for organic and aqueous insulin feed solutions are outlined below.

Total feed solution volume = V

Total solids concentration = C

FORMULATION = weight percents of DPPC/Insulin/citrate as summarized in Table 1.

ORGANIC PHASE SOLUTION PREPARATION:

1. Measure out 200 proof ethanol in amount that is 60 vol% of total feed solution, V.
2. Measure out DPPC in amount that is DPPC wt.% of total solids concentration, C.
3. Add the DPPC into the ethanol and mix with a magnetic stir bar until the DPPC has completely dissolved into solution.

AQUEOUS PHASE SOLUTION PREPARATION:

1. Measure out Sterile Filtered Water in amount that is 40 vol% of total feed solution, V.
2. Measure out citric acid monohydrate in amount that is 8.4 wt.% of total solids concentration, C.
3. Add the citric acid monohydrate into the sterile filtered water and mix with a magnetic stir bar until the citric acid has completely dissolved into solution.
4. Calibrate a pH meter from pH range pH= 4 to pH=7. (Check reading in pH=2.0 buffer, and re-calibrate if pH reading is not pH=2 ± 0.1).
5. Measure the initial pH of the citrate buffer. If the pH is greater than 2.5, adjust the pH to pH=2.5 ± 0.05 with the addition of 1.0 N HCl (hydrochloric acid)
6. Measure out insulin in amount that is Insulin wt.% of total solids concentration, C.*
7. Add insulin into the citrate buffer and mix with a magnetic stir bar until the insulin has completely dissolved into solution.

8. Measure the pH. Adjust the pH = 6.7 ± 0.05 with the addition of 1.0 N NaOH (sodium hydroxide).